"DESIGN AND DEVELOPMENT OF GASTRO-RETENTIVE DRUG DELIVERY SYSTEM"

SYNOPSIS

SUBMITTED FOR REGISTRATION OF

THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN THE SUBJECT

PHARMACEUTICAL SCIENCES

At

SARDAR PATEL UNIVERSITY, BALAGHAT (M.P.)

By

Mr Dinesh Wanjari

M.Pharm.

GUIDE

Dr Rajesh Mujariya

M.Pharm., PhD

INSTITUTE OF PHARMACEUTICAL SCIENCE AND RESEARCH

SARDAR PATEL UNIVERSITY, BALAGHAT (M.P.),

2019-20

INDEX

Sr. No.	Particulars	Page No.
1.	Introduction	3
2.	Literature Review	8
3.	Aim and Objective	10
4.	Plan of Work	11
5.	Reference	12

1. INTRODUCTION

1. Introduction

Oral route of drug administration is the most convenient and commonly used method of drug delivery. However, this route has several physiological problems. Including an unpredictable gastric emptying rate that varies from person to person, a brief gastrointestinal transit time (80-12h), and the existence of an absorption window in the upper small intestine for several drugs.(Badoni A, 2012).

1.1 Factors Controlling Gastric Retention of Dosage Forms **(Nayak AK, 2010)**

The stomach anatomy and physiology contain parameters to be considered in the development of gastroretentive dosage forms. To pass through the pyloric valve in to the small intestine the particle size should be in the range of 1 to 2 mm. The most important parameters controlling the gastric retention time (GRT) of oral dosage forms include :density, size and shape of the dosage form, food intake and its nature, caloric content and frequency of intake, posture, gender, age, sex, sleep, body mass index, physical activity and diseased states of the individual (e.g. chronic disease, diabetes etc.) and administration of drugs with impact on gastrointestinal transit time for example drugs acting as anticholinergic agents (e.g. atropine, propantheline), Opiates (e.g. codeine) and prokinetic agents (e.g. metclopramide, cisapride.). The molecular weight and lipophilicity of the drug depending on its ionization state are also important parameters.

Density of dosage forms

The density of a dosage form also affects the gastric emptying rate and determines the location of the system in the stomach. Dosage forms having a density lower than the gastric contents can float to the surface, while high density systems sink to bottom of the stomach. Both positions may isolate the dosage system from the pylorus. A density of < 1.0 gm/ cm3 is required to exhibit floating property.

Shape and size of the dosage form

Shape and size of the dosage forms are important in designing indigestible single unit solid dosage forms. The mean gastric residence times of nonfloating dosage forms are

highly variable and greatly dependent on their size, which may be large, medium and small units. In most cases, the larger the dosage form the greater will be the gastric retention time (GRT) due to the larger size of the dosage form would not allow this to quickly pass through the pyloric antrum into the intestine.Dosage forms having a diameter of more than 7.5 mm show a better gastric residence time compared with one having 9.9 mm. Ring-shaped and tetrahedron-shaped devices have a better gastric residence time as compared with other shapes.

Food intake and its nature

Food intake, viscosity and volume of food, caloric value and frequency of feeding have a profound effect on the gastric retention of dosage forms. The presence or absence of food in the gastrointestinal tract (GIT) influences the gastric retention time (GRT) of the dosage form. Usually the presence of food in the gastrointestinal tract (GIT) improves the gastric retention time (GRT) of the dosage form and thus, the drugs absorption increases by allowing its stay at the absorption site for a longer period. Again, increase in acidity and caloric value shows down gastric emptying time (GET), which can improve the gastric retention of dosage forms. Effect of gender, posture and age Generally females have slower gastric emptying rates than male. The effect of posture does not have any significant difference in the mean gastric retention time (GRT) for individuals in upright, ambulatory and supine state. In case of elderly persons, gastric emptying is slowed down.

1.2 Advantages of gastro-retentive drug delivery system **(More S, 2018)**

- It increases patient compliance by reducing dosing frequency
- Buoyancy increases gastric residence time
- Better therapeutic effect of short half-life drugs
- Site specific drug delivery to stomach can be achieved
- Gastric irritation can be avoided by designing sustained release.
- No risk of dose dumping by making single unit floating unit such as microspheres releases drug uniformly.
- Delivery of drugs with narrow absorption window in the small intestine region.
- Longer residence time in the stomach could be advantageous for local action in the upper part of the small intestine, for example treatment of peptic ulcer disease.

- Improved bio-availability is expected for drugs that are absorbed readily upon release in the GI tract such as cyclosporine, ciprofloxacin, ranitidine, amoxicillin, captopril,etc.
- Targeted therapy for local ailments in the upper GI tract.

1.3 Disadvantages of gastro-retentive drug delivery system **(More S, 2018)**

- Floating systems has limitation, that they require high levelof fluids in stomach for floating and working efficiently. So more water intake is prescribed with such dosage form.
- In supine posture (like sleeping), floating dosage form may swept away (if not of larger size) by contractile waves. So patient should not take floating dosage form just before going to bed.
- Drugs having stability problem in high acidic environment, having very low solubility in acidic environment and drugs causing irritation to gastric mucosa cannot be incorporated into GRDDS.
- Bio/mucoadhesives systems have problem of high turnover rate of mucus layer, thick mucus layer & soluble mucus related limitations.
- Swellable dosage form must be capable to swell fast before its exit from stomach and achieve size larger than pylorus aperture. It must be capable to resist the housekeeper waves of Phase III of MMC.

1.4 Types of floating drug delivery systems **(Vinod KR, 2010)**

Based on the mechanism of buoyancy and two distinctly different technologies have been utilized in the development of FDDS.

1) Non- Effervescent FDDS

2) Effervescent FDDS

1) Non-Effervescent FDDS

The Non-effervescent FDDS is based on mechanism of swelling of polymer or bioadhesion tomucosal layer in GI tract. The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, hydrophilic gums, polysaccharides and matrix forming materials such as polycarbonate, polyacrylate,

polymethacrylate, polystyrene as well as bioadhesive polymers such as Chitosan and carbopol.

The various types of this system are as:

A. Single Layer Floating Tablets

They are formulated by intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid and maintains bulk density of less than unity. They are formulated by intimate mixing of drug with low-density enteric materials such as CAP, HPMC.

B. Bi-layer Floating Tablets

A bi-layer tablet contain two layer one immediate release layer which releases initial dose from system while the another sustained release layer absorbs gastric fluid, forming an impermeable colloidal gel barrier on its surface, and maintain a bulk density of less than unity and thereby it remains buoyant in the stomach.

C. Alginate Beads

Multi-unit floating dosage forms were developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing precipitation of calcium alginate leading to formation of porous system, which can maintain a floating force for over 12 hours. When compared with solid beads, which gave a short residence time of 1 hour, and these floating beads gave a prolonged residence time of more than 5.5 hours.

D. Hollow Microspheres

Hollow microspheres (microballoons), loaded with drug in their outer polymer shells are prepared by a novel emulsion-solvent diffusion method. The ethanol: dichloromethane solution of the drug and an enteric acrylic polymer is poured into an agitated aqueous solution of PVA that is thermally controlled at 400C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane forms an internal cavity in microsphere of polymer with drug. The microballoons float continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours in vitro.

2) Effervescent System

Effervescent systems include use of gas generating agents, carbonates (ex. Sodium bicarbonate) and other organic acid (e.g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO_2) gas, thus reducing the density of the system and making it float on the gastric fluid. An alternative is the incorporation of matrix

containing portion of liquid, which produce gas that evaporates at body temperature. These effervescent systems further classified into two types.

1. Gas generating systems,
2. Volatile Liquid/Vacuum Containing Systems.

2. LITERATURE REVIEW

2.1 Chandrasekhara RB *et al* (2012) was developed the Ibuprofen Floating tablets optimized gastric floating drug delivery system(GFDDS) by using various polymers like HPMC K4M and Carbopol 940 to enhance the bioavailability and therapeutic efficacy of ibuprofen Various approaches have been followed to encourage gastric retention of an oral dosage form. Floating systems have low bulk density so that they can float on the gastric juice in the stomach. The present work attempts have been made to prepare Ibuprofen by Direct compression method.

2.2 Ashok D *et al* (2012) was studied that the preparation of lipid solid dispersion spray drying technique with gelucire 50/13 and compritol 888 along with HPMC K100M, lactose, sodium bicarbonate and citric acid. The floating tablets was evaluated for uniformity of weight, hardness, friability, drug content, in vitro buoyancy and dissolution studies. The effect of release enhancer on drug release profile and floating properties was investigated. The prepared tablets exhibited satisfactory physico-chemical characteristics. Formulation containing gelucire 50/13 and compritol 888 with HPMC K100M showed good results in invitro buoyancy, but formulation containing gelucire 50/13 and compritol 888 alone failed to float. Increase in the HPMC K100M level was found to increase the floating time of the tablets. From the results it was concluded that famotidine loaded lipid solid dispersion floating tablets prepared by spray drying method was efficient technique for gastro retentive dosage form.

2.3 Jain A *et al* (2011) was studied that the recent advancements and literatures regarding the novel dosage form i.e. the floating drug delivery systems (FDDS) that can be retained in the stomach for a prolonged period of time and gives therapeutic action in a predetermined manner. The methodologies used in the development of FDDS by formulating effervescent and non effervescent floating tablets based on buoyancy mechanism. By utilizing above feasible approaches it is possible to deliver drugs which have narrow therapeutic window.

2.4 Narang N (2011) was studied that the development of rate controlled drug delivery systems to overcome physiological adversities such as short gastric residence times and unpredictable gastric emptying times. Differences in gastric physiology such as gastric pH and motility exhibit both intra and inter subject variability demonstrating significant impact on gastric residence time and drug delivery behavior. This triggered an increased interest towards formulation of novel delivery systems which retained in the stomach for prolonged and predictable period of time. Several approaches such as floating drug delivery systems (FDDS), swelling and expanding systems, bioadhesive systems, modified shape systems, high density systems or other delayed gastric emptying devices.

2.5 Patil P *et al* (2011) was studied that to design the prolong gastric residence time after oral administration. Ofloxacin was a fluoroquinolone antibacterial agent which was highly effective against gram positive and gram negative bacteria. Ofloxacin floating tablets was prepared by wet granulation method incorporating natural polymer like guar gum, locust bean gum, either alone or in combination with HPMC K100M as swelling polymers, with sodium bicarbonate as gas generating agent and were evaluated for parameters such as Weight variation, Hardness, Friability, Drug content, Swelling index, in vitro buoyancy study, in vitro drug release study.

3. AIM AND OBJECTIVE

3.1 Aim

To design and develop Gastro-Retentive Drug Delivery System.

3.2 Objective

1. To provide prolonged and constant therapeutic effect.
2. To reduce the dosing frequency and therefore improve the patient compliance
3. To provide controlled, sustained and targeted delivery of the drug.

4. PLAN OF WORK

4.1. Literature survey

4.2. Procurement of Drugs and Excipients

4.3. Preformulation study

4.4. Formulation of Gastro-Retentive Drug Delivery System

4.6. Evaluation of Gastro-Retentive Drug Delivery System

a) Tablet thickness
b) Hardness
c) Wetting time
d) Weight variation
e) Friability test
f) Floating Time
g) Floating Lag Time
h) Assay for drug content
i) Disintegration time
j) *In-vitro* release Study
k) Stability Studies

4.7 Results and Discussion

5. REFERENCES

Ashok KD and Mohanta GP, 2012, "Formulation and In Vitro Evaluation of Famotidine Floating Tablets By Lipid Solid Dispersion Spray Drying Technique", *International Journal Of Research In Pharmacy And Chemistry*, 2(04):996-1000.

Badoni A, Ojha A, Ganarajan G and Kothiyal P, 2012, "Review on Gastro Retentive Drug Delivery System", *The Pharma Innovation*,1(08):32-42.

Chandrashekhar RB, Vidyadhara S and Ragvendra Rao KV, 2012, "Formulation and Evaluation of Ibruprofen Floating Tablets", *International Journal of Pharmaceutical, Chemical And Biological Sciences*, 2(04):472-481.

Jain AK and Umashankar H, 2011, "A Review on Floating Drug Delivery System", *International Journal of Pharmaceutical Studies And Research*, 2(03):01-06.

More S, Gavali K, Doke O and Kasgawade P, 2018, "Gastroretentive Drug Delivery System", *Journal of Drug Delivery and Therapeutics*, 8(04):24-35.

Narang N, 2011, "An Updated Review On: Floating Drug Delivery System", *Int J App Pharm*, 3(01):1-7.

Nayak AK, Maji R and Das B, 2010, "Gastroretentive drug delivery systems: a review", *Asian Journal of Pharmaceutical and Clinical Research*, 3(01):01-10.

Patil P, Someshwara RB, Kulkarni SV, Basavraj CS and Ammanage A, 2011, "Formulation and In Vitro Evaluation of Floating Matrix Tablets of Ofloxacin", *Asian J. Res. Pharm. Sci.*1(01):17-22.

Vinod KR, Vasa S, Anbuazaghan S, Banji D, Padmasri A and Sandhya S, 2010, "Approaches For Gastrotentive Drug Delivery Systems", *International Journal of Applied Biology and Pharmaceutical Technology*, 1(02):589-601

(Mr Dinesh Wanjari)
M.Pharm.
Research Scholar

Dr D R Mundhada
M.Pharm., PhD
Research Co-Guide

(Dr Rajesh Mujariya)
M.Pharm., PhD
Research Guide